NCI/NIAID/NIST Workshop ‘Dose is More Than a Number’. September 15-16th 2011.

Biological Framework

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Normal tissue response to irradiation is multifactorial

Genetic susceptibility (DNA repair e.g. ATM, NBS1, Rad 51, DNA Pk, Ku). Tissue type specific expression?

Cellular sensitivity

- Multiple cell types
  - Parenchymal cells
  - Endothelial cells
  - Inflammatory cells

- Induced Apoptosis
- DNA/Membrane damage

Tissue related factors

Cytokine induction, e.g. TGF beta, IL-1, IL-6, TNF alpha, bFGF.

- Induced Differentiation
- Cell-Cell Contact
- Cell-Matrix Interactions

- Radical Scavengers e.g.
  - GSH, MnSOD

NIST sept 2011
Issues to be discussed

- Dose response
- Radiobiological effectiveness (RBE)
- Repair of radiation damage and consequent effect of dose rate.
- Differences in different endpoints
- Differences in different tissues
Dose response curves are steep

Lethality due to bone marrow failure (30 day survival)

From Srinivasan et al 2002

Co-60 $\gamma$-rays 1 Gy/min

From Hendry et al 1983

10 MeV electrons 20 Gy/sec
Or Cs $\gamma$-rays at 4.5 Gy/min

Potton 2003

Crypt cell survival and GI tract lethality
Expression of specific genes in irradiated human blood from different donors at 6 or 24 hrs after irradiation.

Relative expression of FDXR (■), CDKN1A (●), PHPT1 (□), BBC3 (▲) and SESN1 (○) at A) 6 and B) 24 hours after irradiation as measured by qRT-PCR.
Cytokine mRNA levels in lung after irradiation

From Johnston et al 1996
Survival curves for different normal tissue cells

Modified from Hall, 1988
Dependence of RBE on type of cell irradiated

From Steel 2002
Cell survival following treatment with different sources (RBE effects)

From Chithrani et al Rad Res 2010
Dose response – teleangiectasia in human skin (Breast Ca patients)

8 MV photons
8-10 MeV electrons
Dose was estimated at 0.1 mm depth.

Bentzen and Overgaard  R and O 1991
RBE effects for different tissues

Fractionation

7.5 MeV neutrons

Low doses

From Field and Hornsey, EJC, 1974
RBE and fractionation

From Joiner and Johns Rad Res 1987
Radiobiological mechanisms underlying the dose rate effects in normal tissues.

Modified from Steel et al (1986)
Crypt cell survival curves
(time between fractions)

From Steel 2002
Dose-rate effects in rat spinal cord: continuous irradiation using $^{192}$Ir- wires (= 6 different constant dose rates)

From Pop et al. IJROBP 1998
Dose-rate effect in murine normal tissues

Figure 12.6 The dose-rate effect in various rodent normal tissues: lung, spinal cord, lip mucosa and bone marrow.

From Joiner and Van der Kogel
Basic Clinical Radiobiology
2009
Effect of (rate of) cell proliferation during LDR irradiation

From Joiner and Van der Kogel
Basic Clinical Radiobiology
2009
Dose response relationship for skin and kidney following fractionated irradiation

From Denekamp 1986
Dose response of lung in different animals

From Hopewell et al. 2000

- Human,
  - Cobalt-60 γ-rays
  - 0.5-4 Gy/min
- Pig,
  - Cobalt-60 γ-rays
  - 0.8-1.4 Gy/min
- Rat,
  - Cobalt-60 γ-rays
  - ?? Gy/min
- Mouse,
  - 240 kVp X-rays
  - 1.8 Gy/min

Figure 2: Dose-related incidence of lungs showing (a) pneumonitis, (b) bronchiolitis (van Dyk et al., 1981), and (c) pulmonary fibrosis (Hermann et al., 1990) in rats (Lehnert and El-Khalil, 1989).
Strain differences in response to lung irradiation

Mice (whole lung)
200 kVp X-rays
@ 0.44 Gy/min

Jackson et al 2010

Rats (hemi lung)
200 kVp X-rays
@ 0.66 Gy/min

Van Eerde et al 2001
Critical Issues

• Steep dose response curves for functional endpoints.
• Dose response may vary for different molecular endpoints.
• Different tissues/cells have different repair capacity. Leads to:
  • Differences in RBE effects
  • Differences in dose rate or fractionation effects.
• Functional tissue endpoints are usually multifactorial due to:
  • Different cell types in the same tissue
    – Parenchymal cells, Stromal cells, Vascular cells.
  • Inflammatory responses
  • Immune responses
  • Tissue ‘repair’ responses
• Strain differences
• Issues of husbandry in lethality studies